

## REMARKS

### I. Notice of Non-Compliant Amendment

The Notice of Non-Compliant Amendment dated April 16, 2008 indicated that the Amendment dated January 14, 2008 was non-compliant because the text of the canceled claims was not deleted as required by 37 CFR § 1.121(c)(4)(i). The Patent Office requires correction of the non-compliance.

Applicants have deleted the text of canceled claims 11-17, 24 and 30-33. Accordingly, applicants submit herewith an updated Amendment A with a revised "Amendments to the claims" section that reflects these changes. No new matter has been added.

Applicants therefore respectfully request withdrawal of the Non-Compliant status of Amendment A and further request that Amendment A be entered into the record and forwarded to the Examiner for consideration.

### II. Status Summary

Claims 1-34 were filed with the subject application. Claims 11-17, 24 and 30-33 have been withdrawn from consideration pursuant to the September 25, 2006 Restriction Requirement. Applicants hereby reserve the right to file one or more patent applications directed to the subject matter of the withdrawn claims. Accordingly, claims 1-10, 18-23, 25-29 and 34 are currently pending and have been examined by the U.S. Patent and Trademark Office (hereinafter "the Patent Office"). Claims 1-10, 18-23, 25-29 and 34 presently stand rejected.

The Patent Office has objected to the priority claim to U.S. Patent Application No. 09/585,077 (now U.S. Patent No. 6,743,823; hereinafter referred to as "the '823 patent"). The Patent Office asserts that the subject matter of claims 25-29 was first disclosed in the instant application and are therefore not given priority based upon the '823 Patent.

The Patent Office has been objected to the specification upon the contention that it contains sequences the lack the appropriate sequence identifier.

Claims 18-23 have been rejected under 35 U.S.C. § 112, second paragraph, upon the Patent Office contention that the claims are indefinite for failure to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Claims 1-4, 6-10, 18-23 and 25-29 presently stand rejected under the provisions of 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,874,471 to Waugh (hereinafter referred to as "Waugh").

Claims 5 and 34 presently stand rejected under the provisions of 35 U.S.C. § 103(a) as allegedly being unpatentable over Waugh in view of U.S. Patent No. 5,767,160 to Kaesemeyer (hereinafter referred to as "Kaesemeyer").

Claims 1-10, 18-23, 25-29 and 34 presently stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of the '823 patent.

The specification has been amended at page 1, line 6, so as to provide the current status of the '823 patent. No new matter has been added.

The specification has been amended at page 49, line 5, to correct a typographical error. Support for this amendment can be found throughout the specification as filed and particularly at page 49, lines 5-11; page 60, line 15 through page 63, line 3; and in Example 3. No new matter has been added.

The specification has also been amended at page 66, lines 13-16, by adding the proper sequence identifiers to the sequences recited therein. Support for the amendment can be found in the Sequence Listing section of the specification and at page 52 of the specification as filed. No new matter has been added.

Claims 11-17, 24 and 30-33 have been canceled. Claims 1, 5, 6, 18 and 25 have been amended to more particularly recite the presently disclosed subject matter. Support for the amendments can be found throughout the specification as filed, including particularly in claim 1 as originally filed; at page 46, line 6, through page 47, line 7; page 48, lines 18-32; page 49, lines 5-11; and in Example 8. No new matter has been added.

New claims 35-38 have been added. Support for new claims 35-38 can be found throughout the specification as filed, including particularly in claims 1, 5, 6, 18, 20, 25 and 27, as originally filed and as currently amended. No new matter has been added.

Reconsideration of the application based on the arguments set forth herein is respectfully requested.

An Information Disclosure Statement is being filed concurrently herewith. It is requested that the reconsideration of this application include consideration of the documents cited in that statement.

### III. Response to the Objection to the Priority Claim

The Patent Office has objected to the priority claim to the '823 patent. In particular, the Patent Office asserts that the '823 patent does not support claims 25-29, and thus contends that the filing date of the instant application (i.e., February 24, 2004) is to be used for the determination of prior art.

After careful consideration of the objection and the Patent Office's bases therefor, applicants respectfully traverse the objection and submit the following remarks.

The Patent Office asserts that claim 25 and claims depending therefrom are drawn to "raising a level of a nitric acid precursor", which was first disclosed in the instant application and are therefore not given priority based upon the '823 patent. In response applicants respectfully submit that the term "nitric acid" as recited in claim 25 and at page 49, line 5, of the specification, is a typographical error. Commensurate with the gist of the instant disclosure, "nitric acid" should be "nitric oxide".

Accordingly, applicants respectfully submit that the specification at page 49, lines 5-11 has been amended hereinabove. In particular, "nitric acid" has been replaced with "nitric oxide". No new matter has been added.

Further, applicants respectfully submit that claim 25 has been amended herein by replacing "nitric acid" with "nitric oxide". Support for this amendment can be found throughout the application as filed, and particularly at page 49, lines 5-11 and in Example 8. No new matter has been added.

As such, applicants respectfully submit that independent claim 25, amended to recite, *inter alia*, "A method of raising a level of nitric oxide precursor in a subject", finds

support in the '823 patent, as conceded by the Patent Office (See, page 10 of the Official Action). Further, applicants respectfully direct the Patent Office's attention to page 60, line 15 through page 63, line 3, particularly at page 62, line 18 through page 63, line 3; and Example 3 of the specification as filed. Accordingly, the subject matter of independent claim 25, and claims 26-29 which depend therefrom, is believed to have been disclosed in the '823 patent and should therefore be accorded an effective filing date of at least June 1, 2000.

Accordingly, applicants respectfully submit that the Patent Office's objection to the priority claim of claims 25-29 to the '823 patent has been addressed. Applicants therefore respectfully request that the instant objection to the priority claim be withdrawn.

#### IV. Response to the Objection to the Specification

The Patent Office has objected to the specification upon the contention that it contains sequences that lack the appropriate sequence identifier. In particular, page 66 of the specification recites two sequences without the proper sequence identifier.

In response, applicants respectfully submit that the proper sequence identifiers have been added to the sequences recited at page 66, lines 13-16. In particular, the "Normal" sequence corresponds to SEQ ID NO:21 and the "Change" sequence corresponds to SEQ ID NO:22. Support for the amendments can be found in the Sequence Listing section of the specification and particularly at page 52 of the Sequence Listing as filed. No new matter has been added.

Accordingly, applicants respectfully submit that the Patent Office's objection to the specification is believed to have been addressed. As such, applicants therefore respectfully request that the instant objection to the specification be withdrawn.

#### V. Response to the 35 U.S.C. §112, Second Paragraph, Indefiniteness Rejection of Claims 18-23

Claims 18-23 have been rejected under 35 U.S.C. § 112, second paragraph, upon the Patent Office contention that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the

invention. Particularly, the Patent Office asserts that claim 18 is indefinite because it is not clear whether the claims are drawn to methods of "treating or preventing" a disorder as set forth in the preamble of claim 18, or to methods that merely require administering a "therapeutically effective amount of a nitric oxide precursor" to any "subject in need thereof," as set forth in the method step of the claim. It is not clear how the method step performed during the practice of the claimed invention actually relates to or results in the particular treatment or prevention set forth in the preamble. Claims 19-23 have been rejected as depending from rejected claim 18.

After careful consideration of the rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

Without conceding to the assertions of the Patent Office, applicants respectfully submit that independent claim 18 has been amended herein to recite, *inter alia*, "A method of treating or preventing pulmonary hypertension..., the method comprising administering to a subject in need thereof a therapeutically effective amount of a nitric oxide precursor, whereby the pulmonary hypertension is treated or prevented. Support for the amendment to claim 18 can be found throughout the specification as filed, including particularly in claims 1 and 5 as originally filed, and on page 46, lines 6-22; and page 48, lines 18-32. No new matter has been added.

As such, applicants respectfully submit that claim 18 is now believed to more clearly recite that the method step performed during the practice of the claimed invention relates to or results in the particular treatment or prevention set forth in the preamble. In particular, applicants respectfully submit that claim 18 is directed to a method of treating or preventing pulmonary hypertension by administering a nitric oxide precursor, whereby the pulmonary hypertension is treated or prevented.

Accordingly, applicants respectfully submit that the asserted indefiniteness in independent claim 18 has been addressed. Applicants further submit that claims 19-23 depend from independent claim 18. As such, applicants respectfully submit that the asserted indefiniteness in these claims has been addressed as well. Accordingly, applicants respectfully request that the instant rejection of claims 18-23 under 35 U.S.C.

§ 112, second paragraph, be withdrawn at this time. A Notice of Allowance is also respectfully requested.

VI. Response to the 35 U.S.C. § 102(b) Rejection  
of Claims 1-4, 6-10, 18-23 and 25-29 Based on Waugh

Claims 1-4, 6-10, 18-23 and 25-29 presently stand rejected under the provisions of 35 U.S.C. § 102(b) as allegedly being anticipated by Waugh. The Patent Office asserts that Waugh teaches each and every element of the rejected claims such that the claims are anticipated.

After careful consideration of the rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that independent claims 1, 18 and 25 have been amended herein to more clearly recite the claimed subject matter. In particular, the amended claims recite that the subjects to be treated suffer from sub-optimal urea cycle function or a condition associated therewith. Claim 1 has been amended to recite a method step of providing a subject under conditions of sub-optimal urea cycle function. Amended independent claim 18 is directed to a method of treating or preventing pulmonary hypertension in a subject suffering from sub-optimal urea cycle function. Finally, independent claim 25, as amended, recites a method of raising a level of a nitric oxide precursor in a subject suffering from sub-optimal urea cycle function. Support for these amendments can be found throughout the specification as originally filed, and particularly in original claim 1 and at page 46, line 6, through page 47, line 7, and particularly at page 46, lines 15-17. No new matter has been added.

By way of non-limiting example, applicants respectfully submit that the specification discloses on pages 46, line 6, through page 47, line 7, that the treatment and prevention methods are designed for subjects under conditions of sub-optimal urea cycle function and/or subjects suffering from conditions related to sub-optimal urea cycle function. To elaborate, the instant methods can pertain to supplementing citrulline in a subject suffering from compromised urea cycle function. In some embodiments, the subject is suffering from a disorder associated with sub-optimal urea cycle function

(e.g., pulmonary hypertension) or is exposed or about to be exposed to an environmental stimulus associated with sub-optimal urea cycle function (e.g., cardiac surgery).

In marked contrast, Waugh, at best, teaches supplementation of citrulline for better health and amelioration of diseases that are not urea-cycle enzyme/substrate liver disorders. See, for example, column 10, lines 41-45, of Waugh. As such, applicants respectfully submit that Waugh does not teach supplementation of citrulline to subjects suffering from sub-optimal urea cycle function, and in fact, explicitly teaches away from the supplementation of nitric oxide precursors such as citrulline to subjects suffering from sub-optimal urea cycle function (i.e., urea-cycle enzyme/substrate liver disorders).

To elaborate, Waugh, at best, could be viewed to teach a method of orthomolecular medicine, wherein citrulline and arginine are supplemented to subjects in substantial amounts that far exceed the daily amounts usually ingested by dietary means. See, for example, the Abstract; column 10, lines 41-60; and column 11, lines 39-52, of Waugh. In contrast, the presently disclosed and claimed methods seek to correct deficiencies in urea-cycle substrates and intermediates due to sub-optimal urea cycle function, not over-supplementation of citrulline to subjects already receiving adequate citrulline. As such, not only does Waugh not teach each and every element of the instant claims, but Waugh teaches a conceptually distinct supplementation regimen designed for fundamentally different purposes.

It is well settled that for a cited reference to qualify as prior art under 35 U.S.C. §102, each element of the claimed invention must be disclosed within the reference. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See also M.P.E.P. § 2131. Applicants respectfully submit that Waugh does not support a rejection any of claims 1, 18 and 25 because each and every element as set forth in the claims is not found, either expressly or inherently described, in Waugh.

As such, applicants respectfully submit that independent claims 1, 18 and 25 have been distinguished over Waugh. Applicants further submit that claims 2-4, 6-10,

19-23 and 26-29 depend from independent claims 1, 18 and 25 . As such, applicants respectfully submit that the rejection of these claims has been addressed as well. Accordingly, applicants respectfully request that the instant rejection of claims 1-4, 6-10, 18-23 and 25-29 under 35 U.S.C. § 102(b) be withdrawn at this time. A Notice of Allowance is also respectfully requested.

VII. Response to the 35 U.S.C. § 103(a) Rejection of Claims 5 and 34 Based on Waugh and Kaesemeyer

The Patent Office has rejected claims 5 and 34 under 35 U.S.C. §103(a) as allegedly being unpatentable over Waugh in view of Kaesemeyer. Particularly, the Patent Office asserts that Waugh teaches each and every element of the rejected claims, except for the administration of citrulline therapy to a subject suffering from pulmonary hypertension (claim 5) or a subject exposed to or about to be exposed to the environmental stimulus of increased postoperative pulmonary vascular tone associated with cardiac surgery (claim 34). However, the Patent Office asserts that Kaesemeyer makes up for the cited deficiencies of Waugh.

Initially, applicants submit that in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation in the references themselves to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. Manual of Patent Examining Procedures (M.P.E.P.) 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Furthermore, even when the combination of references teaches every element of the claimed invention, without a motivation to combine a rejection based on a *prima facie* case of obviousness is improper. *In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). Further, "the level of skill in the art cannot be relied upon to provide the suggestion to combine references". MPEP § 2143.01, citing *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Under these criteria and as



outlined herein below, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness under 35 U.S.C. §103(a) with respect to claims 5 and 34 over the cited references.

As discussed in detail hereinabove, applicants respectfully submit that Waugh does not teach methods of therapy wherein the subject is suffering from sub-optimal urea cycle function. Applicants further submit that Kaesemeyer does not cure this deficiency. Particularly, applicants respectfully submit that in the absence of any teaching or suggestion of treating subjects suffering from sub-optimal urea cycle function in Waugh, it is not believed that the teaching of pulmonary hypertension treatments in Kaesemeyer, as alleged by the Patent Office, is relevant. In Kaesemeyer there does not appear to be any teaching or suggestion of treating subjects suffering from sub-optimal urea cycle function.

As such, applicants respectfully submit that the instant 35 U.S.C. §103(a) rejection of claims 5 and 34 as allegedly being unpatentable over Waugh in view of Kaesemeyer has been addressed. Accordingly, applicants respectfully request that the rejection of claims 5 and 34 be withdrawn at this time. A Notice of Allowance directed to these claims is also respectfully requested.

#### VIII. Response to Obviousness Type Double Patenting Rejections

Claims 1-10, 18-23, 25-29 and 34 have been rejected on the ground of obviousness type double patenting based upon the '823 Patent. The Examiner contends that although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to similar methods and compositions. The Examiner also notes that a non-statutory obviousness-type double patenting rejection can be overcome by filing a terminal disclaimer in compliance with 37 C.F.R. 1.321(c).

Applicants submit herewith a terminal disclaimer in compliance with 37 C.F.R. 1.321(c). In view of the terminal disclaimer, applicants respectfully request withdrawal of the non-statutory obviousness-type double patenting rejection of claims 1-10, 18-23, 25-29 and 34. Applicants further submit that these claims are in condition for allowance and respectfully solicit the same.

In submitting the attached Terminal Disclaimer, applicants do not acknowledge that the subject matter recited in the conflicting claims are not patentably distinct. Moreover, applicants do not acknowledge that the subject matter recited in the rejected claims of the present patent application is an obvious variation of the subject matter recited in one or more claims in the cited U.S. patents. Indeed, the Federal Circuit has noted that a Terminal Disclaimer "is not an admission of obviousness of the later filed claimed invention in light of the earlier filed disclosure for that is not the basis of the Disclaimer." Quad Environmental Technologies v. Union Sanitary District, 20 U.S.P.Q.2d 1392, 1394 (Fed. Cir. 1991).

The Federal Circuit further noted:

In legal principle, the filing of a Terminal Disclaimer simply serves the statutory function of removing the rejection of double patenting and raises neither presumption nor estoppel on the merits of the rejection. It is improper to convert this simple expedient "obviation" into an admission or acquiescence or estoppel on the merit.

Quad Environmental Technologies, 20 U.S.P.Q.2d at 1394-95.

Therefore, with the submission of the Terminal Disclaimer provided herewith, applicants are simply availing themselves of the statutory function of removing the double patenting rejection.

#### IX. Discussion of New Claims 35-38

New claims 35-38 have been added herein as indicated above. Support for new claims 35-38 can be found throughout the specification as filed, including particularly in claims 1, 5, 6, 18, 20, 25 and 27, as originally filed and as currently amended. Further support can be found at page 46, line 6, through page 47, line 7, of the specification as originally filed. No new matter has been added.

Applicants respectfully submit that new claims 35-38 are patentable over the references cited by the Patent Office for the reasons set forth herein above with respect to independent claims 1, 18 and 25. Applicants further respectfully submit that new claims 35-38 are allowable over the cited art of record. None of the cited art, either

alone or in combination, teaches or suggests each and every element of new claims 35-38. Accordingly, allowance of these claims is respectfully requested.

CONCLUSION

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

DEPOSIT ACCOUNT

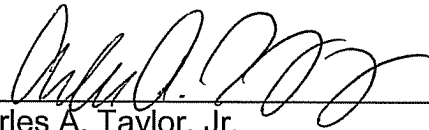
The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: 05/02/2008

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